

23394

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 31/485, 31/165, 45/06	A2	(11) International Publication Number: WO 97/04780 (43) International Publication Date: 13 February 1997 (13.02.97)
(21) International Application Number: PCT/US96/12597 (22) International Filing Date: 31 July 1996 (31.07.96) (30) Priority Data: 08/510,546 2 August 1995 (02.08.95) US (71) Applicant: VIRGINIA COMMONWEALTH UNIVERSITY [US/US]; Medical College of Virginia, MCV Station, 1200 East Marshall Street, Richmond, VA 23298 (US). (72) Inventors: MAYER, David, J.; 502 Honaker Avenue, Rich- mond, VA 23226 (US). PRICE, Donald, D.; 3316 Loxley Road, Richmond, VA 23227 (US). MAO, Jianren; 1630 Monument Avenue, Richmond, VA 23220 (US). LYLE, John, W.; 28 Inlet Terrace, Belmar, NJ 07719 (US). (74) Agents: DILWORTH, Peter, G. et al.; Dilworth & Barrese, 333 Earle Ovington Boulevard, Uniondale, NY 11553 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: PAIN-ALLEVIATING DRUG COMPOSITION AND METHOD FOR ALLEVIATING PAIN (57) Abstract The analgesic effectiveness of a combination drug containing at least one analgesic is significantly enhanced by the addition of a nontoxic N-methyl-D-aspartate (NMDA) receptor antagonist thereto, e.g. dextrometorphan or dextrorphan.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

PAIN-ALLEVIATING DRUG COMPOSITION
AND METHOD FOR ALLEVIATING PAIN

5

BACKGROUND OF THE INVENTION

This invention relates to a pain-alleviating drug composition and method for alleviating pain. The drug composition includes as a first component a first analgesic which may be of the opioid type, e.g., codeine, dihydrocodeine, oxycodone, hydrocodone, meperidine, propoxyphene, pentazocine, etc., or of the nonopioid type, e.g., a coal tar analgesic such as acetaminophen or a nonsteroidal antiinflammatory drug (NSAID) such as aspirin or ibuprofen, as a second component, a sedative, e.g., of the barbiturate type such as butalbital or of the nonbarbiturate type such as diphenhydramine, dichloralphenazone, droperidol or promethazine, a skeletal muscle relaxant such as methocarbamol or carisoprodol and, where the first analgesic is of the opioid type, a second analgesic of the nonopioid type, e.g., acetaminophen, aspirin or ibuprofen, and as a third component, a nontoxic N-methyl-D-aspartate (NMDA) receptor antagonist such as dextrorphan or dextromethorphan.

A number of drug combinations for alleviating pain or treating other conditions associated with a pain component are known including the following: codeine phosphate and acetaminophen; hydrocodone bitartrate and acetaminophen; codeine phosphate and aspirin; hydrocodone bitartrate, acetaminophen, caffeine, chlorpheniramine maleate and phenylephrine hydrochloride; hydrocodone bitartrate and aspirin; dihydrocodeine bitartrate, acetaminophen and caffeine; dihydrocodeine bitartrate, aspirin and caffeine; codeine phosphate and promethazine hydrochloride; meperidine hydrochloride and promethazine hydrochloride; oxycodone hydrochloride and acetaminophen;

oxycodone hydrochloride, oxycodone terephthalate and aspirin; pentazocine hydrochloride and acetaminophen; pentazocine hydrochloride and aspirin; propoxyphene napsylate and acetaminophen; propoxyphene hydrochloride and acetaminophen; propoxyphene hydrochloride, aspirin and caffeine; acetaminophen and diphenhydramine citrate; acetaminophen and diphenhydramine hydrochloride; acetaminophen, dichloralphenazone and isometheptene mucate; aspirin and butalbital; acetaminophen, butalbital and caffeine; aspirin, butalbital and caffeine; codeine phosphate, aspirin, butalbital and caffeine; aspirin and methocarbamol; aspirin and carisoprodol; codeine phosphate, aspirin and carisoprodol; and, fentanyl citrate and droperidol.

The analgesic component(s) of each of these combination drugs can cause adverse reactions. Opioid analgesics such as codeine, dihydrocodeine, oxycodone, hydrocodone, meperidine, propoxyphene and pentazocine can produce tolerance and/or dependence. As for the nonopioid analgesics, acetaminophen has been known to cause fatal hepatic damage and the NSAIDs have a tendency to cause gastrointestinal side effects ranging from the relatively mild to the quite severe (ulceration of the stomach or duodenum). The risk of these adverse reactions is all the greater where their long term administration is concerned.

Dextromethorphan is the d-isomer of the codeine analog of levorphanol. Unlike the l-isomer, dextromethorphan is said to have no analgesic or addictive properties (Goodman and Gilman's, "The Pharmacological Basis of Therapeutics", 8th ed., McGraw-Hill, Inc. (1990), p. 518). The antitussive activity of dextromethorphan has led to its use in a variety of over-the-counter orally administered therapeutic compositions (tablets, syrups) for the relief of cold, influenza and/or cough conditions.

Many, if not most, of these therapeutics also contain a nonopioid analgesic such as an NSAID.

U.S. Patent No. 4,446,140 describes a method of treating mouth pain, i.e., pain or discomfort associated with the oral cavity, the teeth, gums and other mucosal surfaces of the lips, tongue and mouth resulting from such causes as toothache, denture irritations, canker sores, irritation related to inflamed gums, orthodontic tooth manipulation and appliances, oral surgery, etc., by administration of dextromethorphan alone or together with a conventional analgesic such as acetaminophen, indomethacin, ibuprofen or naproxen or a conventional anesthetic such as benzocaine or butacaine.

U.S. Patent No. 5,321,012 discloses that administration of a nontoxic NMDA receptor antagonist such as dextrothorphan or dextromethorphan prior to, with or following administration of an opioid analgesic such as morphine, codeine, and the like, inhibits the development of addiction to and/or dependence on the analgesic.

European Patent Application 0 081 823 describes a method of temporarily reducing pain and discomfort associated with dysmenorrhea by administration of dextromethorphan alone or in combination with one or more additional drugs, e.g., an analgesic such as acetaminophen, indomethacin, ibuprofen or naproxen.

SUMMARY OF THE INVENTION

It has now been found that the analgesic effectiveness of known combination drugs containing at least one analgesic component can be significantly enhanced by the addition of a nontoxic N-methyl-D-aspartate receptor antagonist thereto. In accordance with this invention, a

pain-alleviating drug composition is provided which comprises:

5 a) a pharmacologically effective amount of a first component which is a first analgesic selected from the group consisting of opioid analgesic and nonopioid analgesic;

10 b) a pharmacologically effective amount of a second component which is selected from the group consisting of sedative, skeletal muscle relaxant and, where the first analgesic is of the opioid type, a second analgesic of the nonopioid type; and,

c) an analgesia-enhancing amount of a third component which is a nontoxic N-methyl-D-aspartate receptor antagonist.

15 The foregoing pain-alleviating drug composition is useful for treating a variety of chronic pain and acute pain states, e.g., arthritic pain, lumbosacral pain, musculoskeletal pain, post-operative pain and headache. When, in accordance with the method of the invention, e.g.,
20 a surgical procedure, the drug composition herein is administered to a mammal that is either experiencing pain, e.g., of the aforementioned kind, or is about to be subjected to a pain-causing event, e.g., a surgical procedure, the resulting level of pain relief is
25 significantly enhanced relative to that obtained with the same drug composition but one lacking the nontoxic N-methyl-D-aspartate (NMDA) receptor antagonist component. This ability of the NMDA receptor antagonist component to enhance the efficacy of the analgesic component(s) of the drug
30 composition permits either a reduction in the amount of analgesic(s) in a dosage unit without a reduction in the level of pain relief or an increase in the level of pain relief without an increase in the amount of analgesic(s) in a dosage unit. Either capability offers essentially the
35 same advantage, i.e., less analgesic is required for

effective pain management. Given the adverse effects of the opioid and nonopioid analgesics noted above, such advantage is of considerable benefit to those requiring pain relief, particularly in relatively long term (e.g., 1-4 weeks) or chronic pain situations.

The expression "analgesia-enhancing" refers to any significant improvement in analgesic effectiveness of an analgesic or combination of analgesics expressed in terms of the level of analgesia and/or its duration.

The expression "N-methyl-D-aspartate receptor" shall be understood to include all of the binding site subcategories associated with the NMDA receptor, e.g., the glycine-binding site, the phenylcyclidine (PCP)-binding site, etc., as well as the NMDA channel. Thus, the invention herein contemplates the use of nontoxic substances that block an NMDA receptor binding site, e.g., dextrophan or dextromethorphan, or that block the NMDA channel, e.g., a substance that blocks the magnesium or calcium channel.

The term "nontoxic" as used herein shall be understood in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA for administration to humans. The term "nontoxic" is also used herein to distinguish the NMDA receptor antagonists, or blockers, that are useful in the practice of the present invention from NMDA receptor antagonists such as MK 801 (the compound 5-methyl-10,11-dihydro-SH-dibenze[a,d] cyclohepten-5,10-imine), CPP (the compound 3-[2-carboxypiperazin-4-yl] propyl-1-phosphonic acid) and PCP (the compound 1-(1-phenylcyclohexyl)piperidine) whose toxicities effectively preclude their therapeutic use.

The term "pain-alleviating" shall be understood herein to include the expressions "pain-suppressing" and

"pain-inhibiting" as the invention is applicable to the alleviation of existing pain as well as the suppression or inhibition of pain which would otherwise ensue from an imminent pain-causing event.

5 The expression "combination drug" shall be understood herein to include any drug composition containing at least two therapeutically active components of which at least one is an opioid or nonopioid analgesic drug.

10 BRIEF DESCRIPTION OF THE DRAWINGS

 In the accompanying drawings, Figs. 1 and 2 are graphical presentations of experimental data comparing the analgesic effectiveness of known combination drugs with the same drugs additionally containing dextromethorphan
15 hydrobromide in accordance with the invention and with dextromethorphan hydrobromide administered by itself.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

 The first component of the drug composition of
20 this invention is a first analgesic which can be of the opioid or nonopioid type. Useful opioid analgesics include morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone,
25 propoxyphene, nalmeferene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine, pentazocine and their pharmaceutically acceptable salts. Useful nonopioid analgesics include the coal-tar analgesics, in particular, acetaminophen, and nonsteroidal antiinflammatory drugs
30 (NSAIDs) such as aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, zomepirac,
35 their mixtures and their pharmaceutically acceptable salts.

The second component of the drug composition of this invention can be a sedative (a term used herein to refer to drugs that include not only the sedatives or sedative-hypnotics as such but all other drugs having a sedative action), a skeletal muscle relaxant, a second analgesic which is of the nonopioid type when the first analgesic is of the opioid type or combinations of any of the foregoing. The sedatives include the barbiturate sedatives such as amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, theamylal, thiopental and their pharmaceutically acceptable salts and the nonbarbiturate sedatives include benzodiazepines having a sedative action such as chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam, triazolam and their pharmaceutically acceptable salts, H₁ antagonists having a sedative action such as diphenhydramine, pyrilamine, promethazine, chlorpheniramine, chlorcyclizine and their pharmaceutically acceptable salts, neuroleptics such as droperidol and miscellaneous sedatives such as glutethimide, meprobamate, methaqualone, dichloralphenazone and their pharmaceutically acceptable salts. Skeletal muscle relaxants include baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol, orphenadine and their pharmaceutically acceptable salts.

The third component of the drug composition of this invention is a nontoxic NMDA receptor antagonist. Among the nontoxic substances that block the NMDA receptor and as such are useful for enhancing the analgesic activity of the combination therapeutic in accordance with this invention are dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), their mixtures and their pharmaceutically acceptable salts. Other useful nontoxic

substances that block the NMDA receptor include ketamine, memantine, pyrroloquinoline quinone and cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid. Of the NMDA receptor antagonists, dextromethorphan is preferred for use
5 herein due to its high degree of proven safety and its ready availability (as the hydrobromide salt). While dextrorphan and its pharmaceutically acceptable salts will also provide excellent results, it is not known to be in commercial manufacture at this time.

10 The amounts of first and second component present in a unit dose of the drug composition of this invention can be the same as those employed in comparable dosage forms of known combination drugs such as those previously mentioned. The amount of third component, i.e., the nontoxic NMDA
15 receptor antagonist, will be at least that which is required to significantly enhance the analgesic effectiveness of the analgesic(s) present in the dose. Suitable amounts of NMDA receptor antagonist for a given composition and dosage form can be readily determined employing routine procedures. In
20 general, amounts of NMDA receptor antagonist that will significantly enhance the analgesic effectiveness of the therapeutic composition herein can vary from about 10 to about 100, and preferably from about 15 to about 60, mg per unit dose.

25 All modes of administrations are contemplated for the drug composition of this invention, e.g., administration can be orally, rectally or by intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebro-ventricular injection. The drug composition will ordinarily
30 be formulated with one or more pharmaceutically acceptable ingredients in accordance with known and established practice. Thus, the composition can be formulated as a liquid, powder, elixir, injectable solution or suspension, etc. Formulations for oral use can be provided as tablets,
35 caplets or hard capsules wherein the pharmacologically

active ingredients are mixed with an inert solid diluent such as calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are mixed with an oleaginous medium, e.g., liquid paraffin or
5 olive oil.

Aqueous suspensions can include pharmaceutically acceptable excipients such as suspending agents, e.g., sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate,
10 polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as naturally occurring phosphatide, e.g., lecithin, or condensation products of an alkylene oxide with fatty acids, e.g., polyoxyethylene stearate, or condensation products of ethylene oxide with
15 long chain aliphatic alcohols, e.g., heptadecaethylene-oxyctanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, e.g., polyoxyethylene sorbitol monooleate or condensation products of ethylene oxide with partial esters derived from fatty
20 acids and hexitol anhydrides, e.g., polyoxyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, e.g., ethyl-or-n-propyl-p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose,
25 saccharin or sodium or calcium cyclamate.

In addition to the components already cited, the drug composition herein can contain one or more other pharmacologically active components, e.g., caffeine (a stimulant), chlorpheniramine maleate (an antihistamine),
30 phenylephrine hydrochloride and phenylpropanolamine hydrochloride (decongestants) and isometheptene mucate (a sympathomimetic).

EXAMPLES 1-26

The following unit dosage forms are illustrative
of the pain-alleviating therapeutic composition of this
invention:

	<u>Example</u>	<u>Dosage Form</u>	<u>First Component (mg)</u>	<u>Second Component (mg)</u>	<u>Third Component (mg)</u>	<u>Additional Active Component(s) (mg)</u>
10	1	tablet	codeine phosphate (30)	acetaminophen (650)	dextromethorphan hydrobromide (30)	
15	2	tablet	hydrocodone bitartrate (5)	acetaminophen (500)	dextromethorphan hydrobromide (30)	
	3	tablet	codeine phosphate (30)	aspirin (325)	dextromethorphan hydrobromide (30)	
20	4	tablet	hydrocodone bitartrate (5)	acetaminophen (250)	dextromethorphan hydrobromide (30)	caffeine (30); chlorpheniramine maleate (2); phenylphrine hydrochloride (10)
25	5	tablet	hydrocodone bitartrate (5)	aspirin (500)	dextromethorphan hydrobromide (30)	
30	6	capsule	dihydrocodeine bitartrate (16)	acetaminophen (356)	dextromethorphan (30)	caffeine (30)
	7	tablet	dihydrocodeine bitartrate (16)	aspirin (356)	dextromethorphan hydrobromide (30)	caffeine (30)
35	8	syrup	codeine phosphate (10)	promethazine hydrochloride (6.25)	dextromethorphan hydrobromide (30)	
40	9	injectable	meperidine hydrochloride (25 per ml)	promethazine hydrochloride (25 per ml)	dextromethorphan hydrobromide (10 per ml)	
45	10	capsules	oxycodone hydrochloride (5)	acetaminophen (500)	dextromethorphan hydrobromide (30)	
50	11	tablet	oxycodone hydrochloride (4.5); oxycodone terephthalate (0.38)	aspirin (325)	dextromethorphan hydrobromide (30)	
55	12	caplet	pentazocine hydrochloride (12.5)	aspirin (325)	dextromethorphan hydrobromide (30)	
	13	tablet	pentazocine hydrochloride (12.5)	aspirin (325)	dextromethorphan hydrobromide (30)	
60	14	tablet	propoxyphene napsylate (100)	acetaminophen (650)	dextromethorphan hydrobromide (30)	

	<u>Example</u>	<u>Dosage Form</u>	<u>First Component (mg)</u>	<u>Second Component (mg)</u>	<u>Third Component (mg)</u>	<u>Additional Active Component(s) (mg)</u>
5	15	capsule	propoxyphene hydrochloride (65)	aspirin (389)	dextromethorphan hydrobromide (30)	caffeine (32)
10	16	caplet	acetaminophen (500)	diphenhydramine citrate (38)	dextromethorphan hydrobromide (30)	
15	17	tablet	acetaminophen (500)	diphenhydramine hydrochloride (25)	dextromethorphan hydrobromide (30)	
	18	capsule	acetaminophen (325)	dichloralphen-azone (100)	dextromethorphan hydrobromide (30)	isomet heptene mucate (65)
20	19	tablet	aspirin (650)	butalbital (50)	dextromethorphan hydrobromide (30)	
	20	tablet	acetaminophen (325)	butalbital (50)	dextromethorphan hydrobromide (30)	caffeine (40)
25	21	capsule	aspirin (325)	butalbital (50)	dextromethorphan hydrobromide (30)	caffeine (40)
30	23	tablet	aspirin (325)	methocarbamol (400)	dextromethorphan hydrobromide (30)	
	24	tablet	aspirin (325)	carisprodol (200)	dextromethorphan hydrobromide (30)	
35	25	tablet	codeine phosphate (16)	aspirin (325); carisprodol (200)	dextromethorphan hydrobromide (30)	
40	26	injectable	fentanyl citrate (50 µg (as base) per ml)	droperidol (2.5 per ml)	dextromethorphan hydrobromide (15 per ml)	

In each of these unit doses, the NMDA receptor antagonist dextromethorphan hydrobromide significantly enhances the analgesic activity of the analgesic component(s).

EXAMPLE 27

This example demonstrates the enhanced analgesic effects resulting from the addition of dextromethorphan hydrobromide (DEX) to a drug combination of known type, specifically, one containing as active ingredients codeine hydrochloride (COD) and acetaminophen (APAP).

Each test dosage was administered intra-gastrically to one of four groups (n=10) of test animals, adult male Sprague-Dawley rats each weighing from 350-400g. The analgesia produced by each drug was measured by the tail-flick test of Trujillo et al., Science, 251:85-87 (1991). Tail-flick latencies were tested at one and one half hours after oral administration on Day 1, Day 3, Day 5 and Day 8. Differences in post-administration tail-flick latencies across groups on a given test day were examined using a one-way analysis of variance (ANOVA) followed by post-hoc Waller-Duncan k-ratio t (WD) tests.

One of the following four dosages was administered twice a day to one of the test groups (all dosage amounts in mg/kg body weight): COD(30)+APAP(300), COD(30)+APAP(300)+DEX(50), DEX(50) and saline (control). The observed tail-flick latencies provided a measurement of the analgesic effect for each dosage over the eight day test period. As shown in Fig. 1 and as expected, the DEX(50) and saline (control) dosages were essentially ineffectual as analgesics. The COD(30)+APAP(300) dosage provided an initial response of moderate analgesia but declined significantly thereafter to the point that on Day 8, the dosage provided little effective analgesia. However, in the case of the COD(30)+APAP(300)+DEX(50) dosage, initial analgesic response was significantly higher than that of the COD(30)+APAP(300) dosage and while falling off, continued to provide a significant level of pain relief through Day 8.

EXAMPLE 28

Employing test procedures similar to those described in Example 27, this example shows the enhanced analgesic effects resulting from the addition of DEX to another drug combination of known type, this one containing oxycodone (OXY) and APAP as its active ingredients.

One of the following two dosages was administered twice a day to one of two groups (n=10) of Sprague-Dawley rats: OXY(9)+APAP(585) and OXY(9)+APAP(585)+

DEX(50). As shown in Fig. 2, the OXY(9)+APAP(585) dosage provided an initial level of moderate pain relief and a slight increase therein over the next two days. From Day 3 on, analgesic effectiveness declined sharply and at Day 8, was negligible. In sharp contrast to this dose-response profile, the OXY(9)+APAP(585)+DEX(50) dosage provided a similar level of initial analgesia but one which increased sharply through Day 3, remained at a high level through Day 5 and though declining thereafter, continued to provide a significant level of pain relief at Day 8.

20

WHAT IS CLAIMED IS:

1. A drug composition comprising:
 - a) a pharmacologically effective amount of a first component which is a first analgesic selected from the group consisting of opioid analgesic and nonopioid analgesic;
 - b) a pharmacologically effective amount of a second component which is selected from the group consisting of sedative, skeletal muscle relaxant and, where the first analgesic is of the opioid type, a second analgesic of the nonopioid type; and,
 - c) an analgesia-enhancing amount of a third component which is a nontoxic N-methyl-D-aspartate receptor antagonist.
2. The drug composition of Claim 1 wherein first component (a) is an opioid analgesic and second component (b) is a nonopioid analgesic.
3. The drug composition of Claim 1 wherein first component (a) is an opioid analgesic and second component (b) is a nonopioid analgesic selected from the group consisting of coal tar analgesic and nonsteroidal antiinflammatory drug.
4. The drug composition of Claim 1 wherein first component (a) is a nonopioid analgesic and second component (b) is a sedative selected from the group consisting of barbiturate sedative and nonbarbiturate sedative.
5. The drug composition of Claim 1 wherein first component (a) is a nonopioid analgesic selected from the group consisting of coal tar analgesic and nonsteroidal antiinflammatory drug and second component (b) is a sedative selected from the group consisting of barbiturate sedative and nonbarbiturate sedative.
6. The drug composition of Claim 1 wherein first component (a) is a nonopioid analgesic and second component (b) is a skeletal muscle relaxant.

7. The drug composition of Claim 1 wherein first component (a) is a nonopioid analgesic selected from the group consisting of coal tar analgesic and nonsteroidal antiinflammatory drug and second component (b) is a skeletal muscle relaxant.

8. The drug composition of Claim 1 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

9. The drug composition of Claim 2 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

10. The drug composition of Claim 3 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

11. The drug composition of Claim 4 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

12. The drug composition of Claim 5 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

13. The drug composition of Claim 6 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

14. The drug composition of Claim 7 wherein third component (c) is selected from the group consisting of dextrorphan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

15. The drug composition of Claim 1 wherein first component (a) is an opioid analgesic selected from the group consisting of morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmeferene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine, pentazocine, their mixtures and their pharmaceutically acceptable salts, second component (b) is a nonopioid analgesic selected from the group consisting of acetaminophen, aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, zomepirac, their mixtures and their pharmaceutically acceptable salts and third component (c) is selected from the group consisting of dextrophan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.
16. The drug composition of Claim 1 wherein first component (a) is an opioid analgesic selected from the group consisting of codeine, dihydrocodeine, oxycodone, hydrocodone, meperidine, propoxyphene, pentazocine, their mixtures and their pharmaceutically acceptable salts, second component (b) is a nonopioid analgesic selected from the group consisting of acetaminophen, aspirin, ibuprofen, their mixtures and their pharmaceutically acceptable salts and third component (c) is selected from the group consisting of dextrophan, dextromethorphan, their mixtures and their pharmaceutically acceptable salts.

17. The drug composition of Claim 5 wherein
second component (b) is a sedative selected from the group
consisting of butalbital, diphenhydramine,
dichloralphenazone, promethazine, droperidol, their mixtures
5 and their pharmaceutically acceptable salts and third
component (c) is selected from the group consisting of
dextrorphan, dextromethorphan, their mixtures and their
pharmaceutically acceptable salts.

18. The drug composition of Claim 7 wherein
10 second component (b) is a muscle relaxant selected from the
group consisting of methocarbamol, carisoprodol,
orphenadrine, chlorzoxazone, their mixtures and their
pharmaceutically acceptable salts and third component (c) is
selected from the group consisting of dextrorphan,
15 dextromethorphan, their mixtures and their pharmaceutically
acceptable salts.

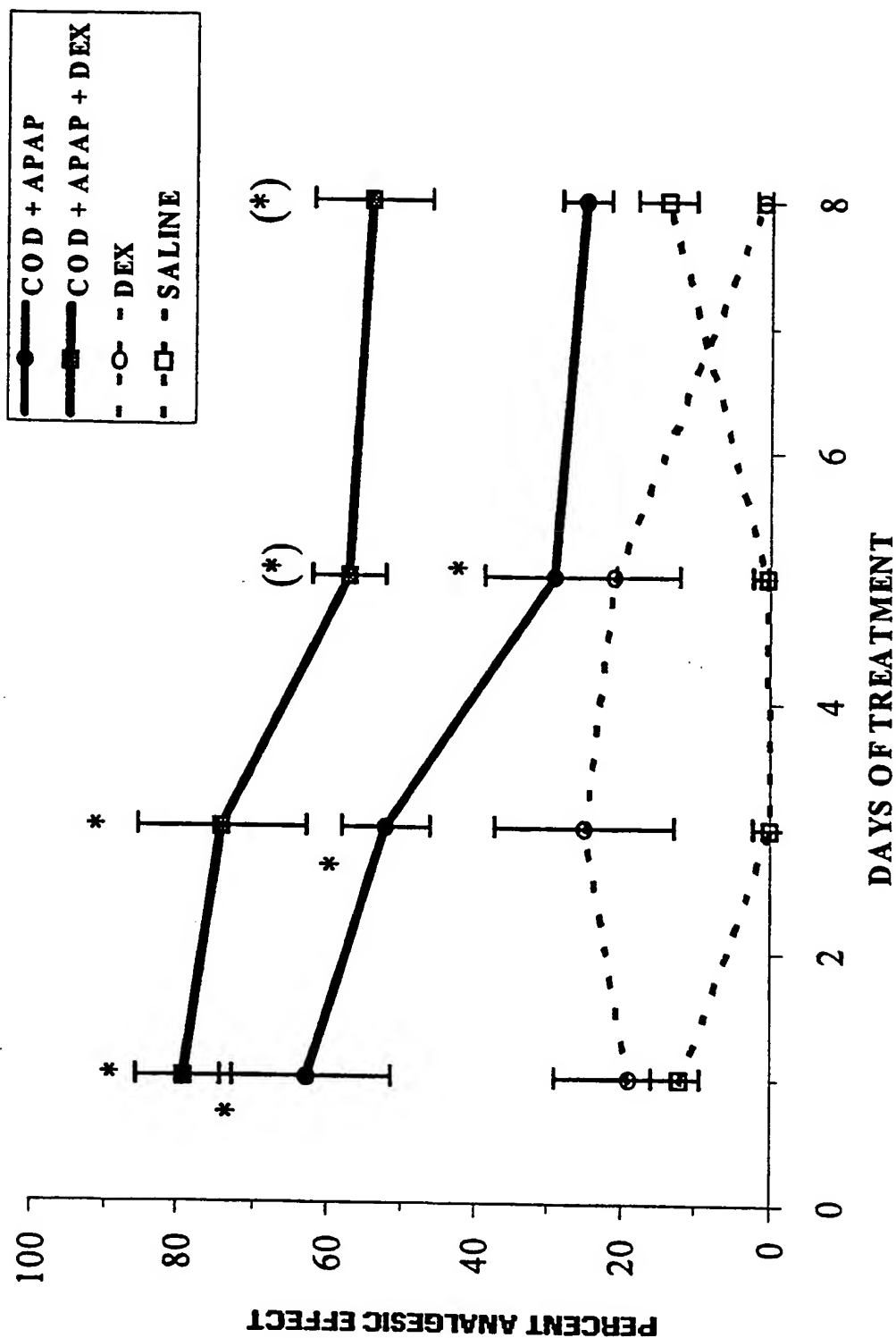
19. A method for alleviating pain which comprises
administering to a mammal which is either experiencing pain
or is about to be subjected to a pain-causing event a pain-
20 alleviating amount of a drug composition comprising:

- a) a pharmacologically effective amount of a
first component which is a first analgesic selected from the
group consisting of opioid analgesic and nonopioid
analgesic;
- 25 b) a pharmacologically effective amount of a
second component which is selected from the group consisting
of sedative, skeletal muscle relaxant and, where the first
analgesic is of the opioid type, a second analgesic of the
nonopioid type; and,
- 30 c) an analgesia-enhancing amount of a third
component which is a nontoxic N-methyl-D-aspartate receptor
antagonist.

20. The method of Claim 19 wherein the pain is
arthritic pain, lumbosacral pain, musculoskeletal pain,
35 post-operative pain or headache.

1 / 2

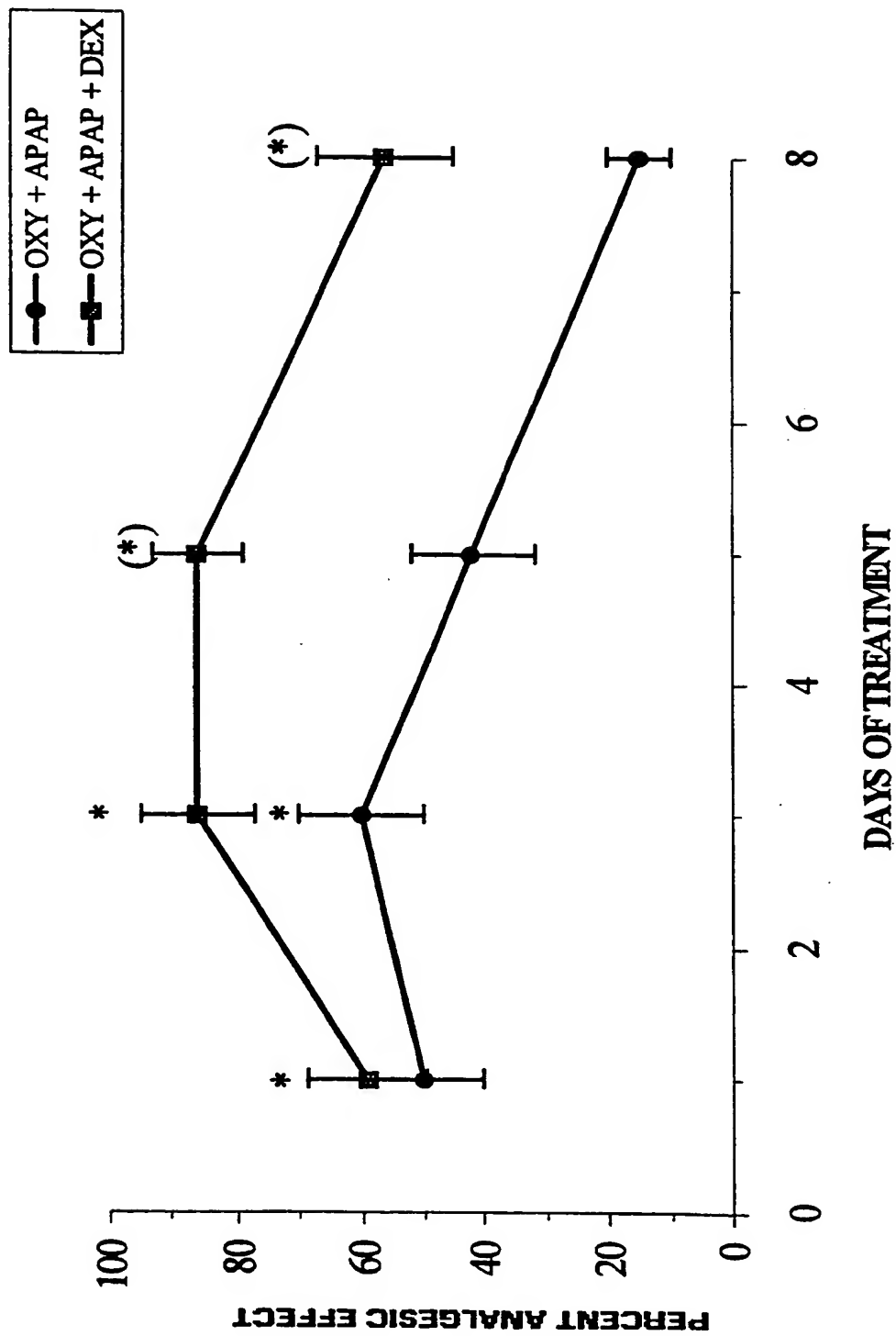
Figure 1.



SUBSTITUTE SHEET (RULE 26)

2 / 2

Figure 2.



SUBSTITUTE SHEET (RULE 26)

THIS PAGE BLANK (USPTO)

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/485, 45/06, 31/165 // (A61K 31/485, 31:485, 31:165)	A3	(11) International Publication Number: WO 97/04780 (43) International Publication Date: 13 February 1997 (13.02.97)
(21) International Application Number: PCT/US96/12597 (22) International Filing Date: 31 July 1996 (31.07.96) (30) Priority Data: 08/510,546 2 August 1995 (02.08.95) US (71) Applicant: VIRGINIA COMMONWEALTH UNIVERSITY [US/US]; Medical College of Virginia, MCV Station, 1200 East Marshall Street, Richmond, VA 23298 (US). (72) Inventors: MAYER, David, J.; 502 Honaker Avenue, Rich- mond, VA 23226 (US). PRICE, Donald, D.; 3316 Loxley Road, Richmond, VA 23227 (US). MAO, Jianren; 1630 Monument Avenue, Richmond, VA 23220 (US). LYLE, John, W.; 28 Inlet Terrace, Belmar, NJ 07719 (US). (74) Agents: DILWORTH, Peter, G. et al.; Dilworth & Barrese, 333 Earle Ovington Boulevard, Uniondale, NY 11553 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i> (88) Date of publication of the international search report: 27 March 1997 (27.03.97)
(54) Title: PAIN-ALLEVIATING DRUG COMPOSITION AND METHOD FOR ALLEVIATING PAIN (57) Abstract The analgesic effectiveness of a combination drug containing at least one analgesic is significantly enhanced by the addition of a nontoxic N-methyl-D-aspartate (NMDA) receptor antagonist thereto, e.g. dextrometorphan or dextroprophan.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/12597

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/485 A61K45/06 A61K31/165 //(A61K31/485,31:485,31:165)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 615 749 A (UNIV VIRGINIA COMMONWEALTH) 21 September 1994 see claims 1-3,6,8 see column 7, line 54-58 ---	1-20
Y	EP 0 081 823 A (NELSON RES & DEV) 22 June 1983 cited in the application see claims 7,8,11 ---	1-20
Y	US 5 321 012 A (MAYER DAVID J ET AL) 14 June 1994 cited in the application see the whole document ---	1-3, 8-10,15, 16,19,20
Y	US 4 446 140 A (NELSON ERIC L) 1 May 1984 cited in the application see the whole document ---	1-20
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

11 February 1997

Date of mailing of the international search report

21.02.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stierman, B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/12597

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 96 07412 A (UNIV VIRGINIA COMMONWEALTH) 14 March 1996 see the whole document ---	1-20
P,Y	BRAIN RES, vol. 699, no. 1, 13 November 1995, pages 157-160, XP002025010 C. ADVOKAT ET AL.: "Potentiation of morphine-induced antinociception in acute spinal rats by the NMDA antagonist dextrorphan" see the whole document ---	1-3, 8-10,15, 16,19,20
Y	DATABASE WPI Section Ch, Week 9304 Derwent Publications Ltd., London, GB; Class B02, AN 93-027343 XP002025013 & CA 1 311 486 C (AMERICAN HOME PROD CORP) , 15 December 1992 see abstract ---	1-3, 8-10,15, 16,19,20
Y	WO 93 17673 A (TOP GOLD PTY LIMITED) 16 September 1993 see claims 11,12 ---	1-5, 8-12, 15-17, 19,20
Y	EP 0 193 355 A (LILLY CO ELI) 3 September 1986 see the whole document ---	1-3, 8-10,15, 16,19,20
Y	BUNDESVERBAND D. PHARM. IND. E.V.: "ROTE LISTE 1987" 1987, EDITIO CANTOR, AULENDORF/WÜRTT. XP002025011 see no. 63025: "Paraflex spezial" see no. 63026: "Robaxisal" ---	1,6-8, 13,14, 18-20
Y	BUNDESVERBAND D. PHARM. IND. E.V.: "ROTE LISTE 1987" 1987, EDITIO CANTOR, AULENDORF/WÜRTT. XP002025012 see no 05188: "Aequiton" -----	1,4,5,8, 11,12, 17,19,20

INTERNATIONAL SEARCH REPORT

I national application No.

PCT/US 96/ 12597

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 19-20
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.: 1-20
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:

Please see next page.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Compounds are not sufficiently defined as "opioid analgesic", "nonopioid analgesic", "sedative", "skeletal muscle relaxant", "nontoxic N-methyl-D-aspartate receptor", "coal tar analgesic", "nonsteroidal antiinflammatory drug", "barbiturate sedative", "nonbarbiturate sedative", etc. As for many of the specific compounds mentioned in the claims, no pharmacological data is given and they only form a large enumeration of compounds, the search had to be restricted for economic reasons as well as for reasons of obscurity (Art.6 PCT). The search has been restricted to the compounds for which pharmacological data is given and to the general inventive concept.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/12597

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0615749	21-09-94	US-A- 5352683 CA-A- 2115792 JP-A- 7002671 US-A- 5502058	04-10-94 06-09-94 06-01-95 26-03-96
EP-A-0081823	22-06-83	AU-B- 557966 AU-A- 9133782 CA-A- 1194799 JP-A- 58109420 US-A- 4446140	15-01-87 16-06-83 08-10-85 29-06-83 01-05-84
US-A-5321012	14-06-94	CA-A- 2113515 EP-A- 0608893 JP-A- 7133231 US-A- 5556838	29-07-94 03-08-94 23-05-95 17-09-96
US-A-4446140	01-05-84	AU-B- 557966 AU-A- 9133782 CA-A- 1194799 EP-A- 0081823 JP-A- 58109420	15-01-87 16-06-83 08-10-85 22-06-83 29-06-83
WO-A-9607412	14-03-96	AU-A- 3460495	27-03-96
WO-A-9317673	16-09-93	NONE	
EP-A-0193355	03-09-86	AU-B- 584681 AU-A- 5400186 CA-A- 1267092 DE-A- 3684626 JP-B- 7045405 JP-A- 61200911 US-A- 4683235	01-06-89 28-08-86 27-03-90 07-05-92 17-05-95 05-09-86 28-07-87

THIS PAGE BLANK (USPTO)